
Anaphylaxis: a 7-year follow-up survey of 46 children

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Background: Little is known about the frequency of and the features associated with recurrent anaphylaxis in pediatric populations. During 1994 to 1996, we enrolled 76 children affected by anaphylaxis in a prospective study to analyze their clinical and allergic features.

Objective: To undertake a follow-up study of these children to ascertain how many experienced a recurrence of anaphylaxis.

Methods: After a mean interval of 7 years, a pediatric allergist conducted a telephone interview of patients who had been enrolled in our 1994-1996 study.

Results: A telephone interview was successfully completed in 46 (61%) of the 76 patients who had been enrolled in our 1994-1996 study. Of these 46 patients, 14 (30%) had experienced a recurrence of anaphylaxis. Children with atopic dermatitis either during 1994 to 1996 (64% vs 34%; $P = .04$) or at the time of the current study (43% vs 16%; $P = .03$) and those with urticaria-angioedema at the time of the current study (93% vs 31%; $P = .0002$) were found to be at a significantly higher risk for recurrent anaphylaxis. Furthermore, those children who were sensitive to at least 1 food allergen during 1994 to 1996 were more likely to have experienced a recurrence of anaphylaxis (93% vs 56%; $P < .04$).

Conclusions: This study suggests that patients may have a greater risk of recurrence of anaphylaxis if they have atopic dermatitis, urticaria-angioedema, or at least 1 positive result of skin prick tests to food allergens.

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INTRODUCTION

Anaphylaxis is an unusual but not rare event, both in adults¹⁻³ and in children.^{4,5} Usually, an accurate diagnosis enables the patient to avoid triggering factors and therefore eliminate subsequent episodes of anaphylaxis. Some subjects, however, experience multiple anaphylactic episodes even after accurate diagnosis and treatment. Despite the extensive literature on anaphylaxis, little is known about the characteristics of patients with a tendency to experience recurrent anaphylaxis. To investigate the frequency of and the features associated with recurrent anaphylaxis in a pediatric population, we conducted a telephone survey (questionnaire) in a cohort of well characterized children who had been referred to us because of anaphylaxis between 1994 and 1996.⁵

Briefly, in that study we found that 79% of the 76 children studied had at least 1 positive result of a skin prick test to one or more of the common inhalant or food allergens. Children with venom-induced anaphylaxis usually had negative results of skin tests to the allergens tested ($P < .001$). Younger age ($P < .001$) and eczema ($P = .01$) were more frequently found among children with food-dependent anaphylaxis, whereas older age ($P = .005$) and urticaria-angioedema ($P < .01$) were common among those with exercise-induced anaphylaxis.

Skin and respiratory manifestations had an earlier onset and were more common than gastrointestinal and cardiovascular manifestations. In children with food-associated ana-

phylaxis, the most frequent clinical manifestation ($P = .001$) was gastrointestinal symptoms, whereas cardiovascular symptoms were rare ($P < .05$). The most probable causative agents in the 95 anaphylactic episodes described were foods (57%), Hymenoptera venom (12%), drugs (11%), exercise (9%), vaccines (2%), additives (1%), specific immunotherapy (1%), and latex (1%), but in 6 cases (6%), the agent was never determined. Among the foods, seafood and milk were the most frequently involved. Sixty-two percent of the patients were treated in the emergency department or the hospital.

SUBJECTS AND METHODS

Previously, we described the clinical and allergic features of 76 children affected by anaphylaxis.⁵ In our previous study, we prospectively considered patients with anaphylaxis referred between 1994 and 1996 to the Allergy Unit of A. Meyer Children's Hospital (Florence, Italy). Those children who had at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents were included in the study. Every child underwent skin prick tests with extracts from a panel of foods and the most common inhalant substances. When necessary, additional skin tests and oral challenges were also performed.

We attempted to contact by telephone all 76 children with anaphylaxis enrolled in our previous prospective study. If the patient was still younger than 18 years (adult age in Italy), a parent of the child was interviewed; if the patient was 18 years old or older, the patient was interviewed. In either situation, a trained pediatric allergist performed the interview. Verbal informed consent was obtained, and confidentiality of study participants was strictly preserved.

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Table 1. Characteristics of 46 Patients with Previous Anaphylaxis Who Participated in Current Survey

Characteristic	No. (%) or mean $\pm$ SD (range)
Male:female	28:18 (61:39)
Follow-up time from first episode, y	7.0 $\pm$ 1.05 (5–8.6)
Actual age, y	14.0 $\pm$ 4.92 (7–26)
Age at first episode, y	5.8 $\pm$ 4.9 (1–18)
Recurrent anaphylaxis	14 of 46 (30)

For the survey, patients were asked the following questions: (1) whether they had experienced another episode of anaphylaxis, as we previously defined (that is, had at least 2 of the 3 aforementioned main indicators of anaphylactic reaction—hypotension, inspiratory dyspnea, and urticaria-angioedema—within 2 hours after exposure to one of the most probable causative agents)⁵; (2) whether during the past 12 months a physician had diagnosed asthma, rhinitis, atopic dermatitis (AD), or urticaria-angioedema not associated with an anaphylactic episode (OA); (3) whether they were carrying epinephrine; (4) whether epinephrine had been prescribed when the diagnosis of anaphylaxis was made; (5) whether they were still consuming a restricted diet, if they had food-induced anaphylaxis; (6) whether they had immunotherapy for Hymenoptera venom; and (7) whether they were currently receiving antiallergy therapy, such as H₁-antihistamine, bronchodilator, or inhaled corticosteroid.

We recorded AD, asthma, rhinitis, or OA as present at the time of the study if a physician had diagnosed those conditions during the previous 12 months. The collected data were entered into our database, along with the clinical and allergic features of the children at the time of initial examination in our unit. The data were analyzed with the statistical program SPSS 4.0 for Windows (SPSS Inc, Chicago, IL). The children were categorized as positive or negative on the basis of the recurrence of anaphylaxis. The relationships between the recurrence of anaphylaxis and other characteristics, including number of anaphylactic episodes, were analyzed by logistic regression or the χ^2 test. A *P* value less than .05 was considered significant.

RESULTS

During 1994 through 1996, we had enrolled 76 children affected by anaphylaxis in a prospective study to analyze their clinical and allergic features.⁵ After a mean duration of

7 years, we were able to interview 46 of them (61%) by telephone to investigate their clinical outcome. At the time of the current study, only 10 of the original study participants (13%) were still undergoing follow-up in our unit.

The characteristics of the 46 available patients who participated in our current survey are summarized in Table 1. For 30 of the children enrolled in our previous study, our records contained invalid telephone numbers or addresses; despite a thorough search of the telephone directory, it was not possible to contact them. (We record only the name of the pediatric patient. If there is a change of address or telephone, the telephone company reports only the name of the head of the family, usually the father.)

Of the 46 patients interviewed, 14 (30%) had experienced a recurrence of anaphylaxis (10 patients experienced a single recurrence, 2 had 2 recurrent episodes, 1 had 3 recurrences, and 1 had 4 recurrences). None of the patients died or experienced biphasic anaphylaxis. Nine of the 14 patients with recurrent anaphylaxis (64%) went to the emergency department and spent 24 to 48 hours in the hospital; 12 patients received epinephrine within the first 30 minutes after the beginning of the anaphylactic episode, 5 by self-injection and 7 at the hospital.

No statistically significant association was found between recurrent anaphylaxis and sex of the patient (*P* = .29), age at the time of the first episode (*P* = .53), and actual age (*P* = .45). Even those patients who had more than 1 anaphylactic episode between 1994 and 1996 were not at a greater risk of having recurrent anaphylaxis (*P* = .30). Certain clinical features of the 46 subjects during the current survey and during the previous study (1994–1996) are summarized in Table 2.

The percentage of children with other atopic diseases as predictors of a recurrence of anaphylaxis is depicted in Figure 1. Children with AD either during the 1994 to 1996 study or at the time of the current study and those with OA at the time of the current study were at significantly higher risk for having recurrent anaphylaxis. At the time of the current study, no association was found between having either rhinitis [17 (53%) of the 32 patients with no recurrence of anaphylaxis had rhinitis at the time of the study compared with 9 of 14 (64%) with recurrent anaphylaxis (*P* = .36)] or asthma [13 (41%) of the 32 patients with no recurrence of anaphylaxis had asthma compared with 7 of 14 (50%) with recurrent anaphylaxis (*P* = .36)]. Even the children who had asthma or rhinitis during the 1994 to 1996 study did not have

Table 2. Clinical Features of 46 Children during 1994 to 1996 Study and during Current Survey

Feature	No. (%) of children		
	1994 to 1996	Current survey	1994 to 1996 and currently
Urticaria-angioedema	22/46 (47)	23/46 (50)	14/46 (30)
Atopic dermatitis	20/46 (43)	11/46 (24)	9/46 (20)
Asthma	20/46 (43)	20/46 (43)	14/46 (30)
Rhinitis	13/46 (28)	26/46 (57)	7/46 (15)
Skin sensitivity			
To at least 1 food allergen	31/46 (67)	Not studied	
To at least 1 inhalant allergen	33/46 (72)	Not studied	

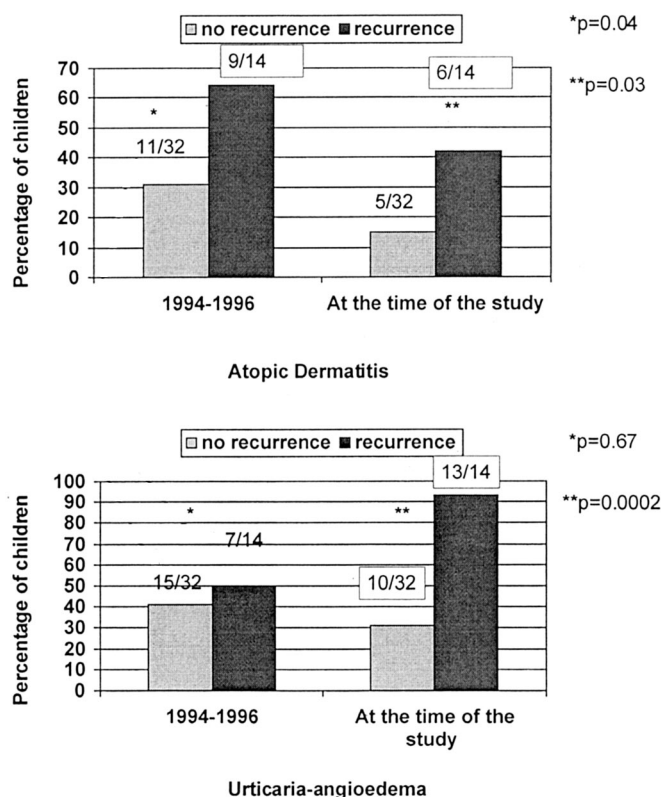


Figure 1. Top, Prevalence of atopic dermatitis (AD) in children with or without recurrence of anaphylaxis. Compared with the 32 patients who had no recurrence of anaphylaxis, the 14 with at least a single recurrence of anaphylaxis more often experienced AD during 1994 to 1996 and were also experiencing AD more frequently at the time of the current study. Bottom, Prevalence of urticaria-angioedema in children with or without recurrence of anaphylaxis. The 14 patients with at least a single recurrence of anaphylaxis were experiencing urticaria-angioedema more often at the time of the current study compared with the 32 who had no recurrence of anaphylaxis. No significant difference was found between the 2 groups in the prevalence of urticaria-angioedema during the 1994 through 1996 study.

recurrent anaphylaxis more often than did those without these conditions (data not shown). Furthermore, an important risk factor seemed to be skin sensitivity to at least 1 food allergen at the time of initial evaluation. Indeed, those patients who were sensitive to at least 1 food allergen during 1994 to 1996 were more likely to have recurrent episodes of anaphylaxis than were those without this sensitivity [13 (93%) of 14 patients vs 18 (56%) of 32; $P < .04$ with the χ^2 Fisher 2-tailed exact test].

At the time of the current survey, 85% of the children were taking antihistamines, bronchodilators, inhaled corticosteroids, or some combination of these drugs. Children with recurrent anaphylaxis were taking antiallergy drugs more often than those without recurrent episodes, although the difference did not reach statistical significance [14 (100%) of 14 vs 25 (78%) of 32; $P = .15$ with the χ^2 Fisher 2-tailed exact test].

At the time of the first evaluation, all children were prescribed self-injectable epinephrine (Fastjekt; Bracco, Milan)

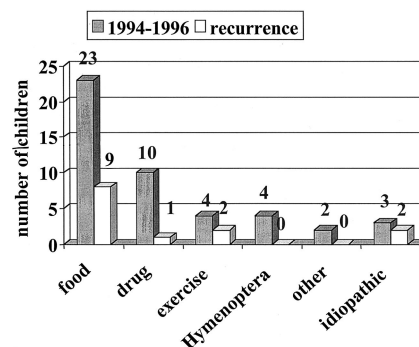


Figure 2. Principal causes of anaphylaxis during the 1994 through 1996 study and number of patients with recurrent anaphylaxis after 7 years.

at a dose of 0.15 mg if the child weighed less than 30 kg and at 0.3 mg if heavier than 30 kg. At the time of follow-up, however, only 39% (18 of 46) still had self-injectable epinephrine available at home. Of the other 28 patients, 14 (50%) no longer thought that it was necessary, 4 (14%) believed that it was dangerous, 2 (7%) had parents that did not want their children to feel different from their peers, 2 (7%) forgot to buy it, and 2 (7%) indicated that their primary care pediatrician said it was not necessary. The other 4 patients (14%) were unable to provide an explanation. Those children who experienced recurrent anaphylaxis did not have epinephrine available more often than did those who had no such recurrences [6 (43%) of 14 vs 12 (38%) of 32; $P = .79$ with the χ^2 test]. Only 10 of the 46 children who completed the current study had visited our office during the previous 12 months. Frequently, the patients did not live nearby, and they came to our office only for diagnosis and then underwent follow-up by a local allergist or directly by a general practitioner. Nine of the 10 children who had visited our office during the previous 12 months had epinephrine available at home ($P < .001$ with the χ^2 Fisher 2-tailed exact test).

The reported major causes of anaphylaxis during the 1994 through 1996 study and the number of children who experienced a recurrence of anaphylaxis are summarized in Figure 2. Of the 46 children, 14 (30%) had experienced a recurrence of anaphylaxis. The specific causes were not significantly associated with the risk of recurrence of anaphylaxis. We noted, however, that 9 of 23 children with previous food-related anaphylaxis, 2 of 4 children with previous exercise-related anaphylaxis, and 2 of 3 children who experienced idiopathic anaphylaxis had at least 1 recurrence. Children with previous food-associated anaphylaxis had had anaphylactic episodes due to milk (10 cases), vegetables (7 cases), fish (4 cases), nuts (3 cases), and eggs (2 cases). Among those children with anaphylaxis attributable to food, the recurrences were usually (in 7 of 9 cases) caused by the same food—milk in 4 cases, oats in 1 case, fish in 1 case, and kiwi in 1 case. In 2 cases, the recurrent anaphylaxis was due to a food unrelated to the food item responsible for the first episode of anaphylaxis. In one case, a child with polysensi-

tive allergy who had a previous anaphylactic episode attributable to milk experienced a mild anaphylaxis the second time he ate kiwi, to which he was not known to be allergic. In another case, a child with a previous anaphylaxis to nuts had an anaphylactic episode due to the concurrent ingestion of wheat, milk, and tomato (pizza)—he was allergic to all of these items but had tolerated them when they were ingested separately. All 23 children with anaphylaxis due to food were still consuming a restricted diet designed to avoid the food to which they were allergic. All children with Hymenoptera venom-induced anaphylaxis underwent immunotherapy. In 2 cases, a re-sting caused no reaction.

DISCUSSION

Anaphylaxis can occur in both adults and children¹⁻⁵ and is a potentially fatal event.⁶⁻⁸ The prevalence is estimated to be 150 to 190 cases per 1 million hospitalized patients,⁹ with a 2% mortality rate. A similar mortality rate has been reported among pediatric populations.¹⁰ Primary prevention is impossible because no marker exists to identify patients at risk for experiencing anaphylaxis. Currently, only secondary prevention based on the avoidance of a known triggering agent is possible. Furthermore, the consequences and the severity of such episodes can be minimized by the availability of epinephrine, the only known lifesaving treatment for an acute episode of anaphylaxis.⁸

An appropriate and efficacious secondary prevention is based on an accurate diagnosis and a thorough knowledge of the risks and probability of recurrence of the condition. The clinical features of anaphylaxis have recently been described in many studies, and the major reported triggering agents are food, drugs, Hymenoptera venom, immunotherapy, latex, and exercise.^{1,2,4,5} In children, the major causes have been reported to be various foods, whereas in adults, drugs have a more important role.^{1,5,11} Unfortunately, the diagnosis is often not straightforward, especially when the affected patient has been in contact with several potential triggering factors, such as many foods or drugs, before an anaphylactic episode. Often, despite long and thorough testing, a causative agent cannot be identified, and the anaphylaxis is labeled as idiopathic.¹²

Little is known about the natural history of anaphylaxis. Indeed, anaphylaxis is not a frequent event, and many of the available studies on anaphylaxis are either retrospective or based on emergency department evaluation. Follow-up of those studies is difficult, inasmuch as the first evaluation and treatment may not have been homogeneous and may influence the likelihood of recurrent episodes.

A study has been performed on the natural history of exercise-induced anaphylaxis, based only on a validated questionnaire.¹³ This study showed that the frequency of the episodes tends to stabilize or decrease over time. To our knowledge, no other study has been performed thus far to identify characteristics and risk factors associated with recurrent anaphylaxis in children.

In our current study, we evaluated a population of children who had been prospectively enrolled in a study during 1994

to 1996 at a mean interval of 7 years after the first episode of anaphylaxis.⁵ A standardized evaluation had been conducted at the same medical center by a pediatric allergist. In a follow-up study, 6 to 8 years after the first evaluation, 46 (61%) of the original 76 children were available for a telephone interview.

Of the 46 children, 14 (30%) had experienced a further episode of anaphylaxis, but none of them had died or had experienced a biphasic event. In a retrospective study of 109 patients with anaphylaxis admitted to a pediatric hospital, Lee and Greenes¹⁰ found a low prevalence of deaths (2%) and biphasic anaphylaxis (6%). In light of the small number of cases reported in the current study, we might have missed these 2 events. Nevertheless, because all our patients had experienced a previous episode of anaphylaxis, we speculate that they probably would have sought treatment in an efficient and appropriate manner, which may have limited a potential biphasic event or a deadly course. Indeed, Lee and Greenes¹⁰ found that children who did not receive epinephrine within the first 30 minutes of an anaphylactic episode were more at risk of having biphasic anaphylaxis; 12 of 14 of our studied patients with recurrent anaphylaxis received epinephrine within the first 30 minutes after onset of such an episode.

In our study, patients more at risk for a recurrence of anaphylaxis were those who had AD, OA, or at least a positive result of a skin prick test to food during our 1994 to 1996 study. In our previous study, we also showed that AD was a risk factor for the development of food-related anaphylaxis, and Shadick et al¹³ have emphasized that patients with eczema have an increased risk for a recurrence of exercise-induced anaphylaxis. Furthermore, Vander Leek et al¹⁴ reported that 52% of children with peanut-associated AD subsequently experienced anaphylaxis.

Our findings confirm that prevention of recurrent episodes in children with food-related anaphylaxis and AD is particularly challenging. Accidental ingestion of food known to be a triggering factor for anaphylaxis is not rare, and sometimes food previously tolerated can subsequently precipitate anaphylaxis. Indeed, children who have experienced food-related anaphylaxis are often highly allergic patients in whom anaphylaxis to a variety of foods may develop. Interestingly, in a series of pediatric cases of fatal or near-fatal anaphylaxis, all children were allergic to a specific food and ingested, without awareness of it, the food to which they were allergic.¹⁵ Children with OA and a previous episode of anaphylaxis should undergo meticulous follow-up. The presence of OA may be a sign that their mast cells and basophils have high releasability.¹⁶⁻¹⁸

Asthma has been reported to be present frequently in children with fatal or near-fatal anaphylaxis.¹⁵ In our study, we found no association between asthma and recurrent anaphylaxis. The prevalence of asthma in our study population was high (43%). Because of the small number of patients who experienced recurrence of anaphylaxis, our study did not have the statistical power to determine whether food-related asthma was a risk factor for recurrent anaphylactic episodes. Children with food-induced, exercise-related, or idiopathic anaphylaxis had a higher recurrence rate, but the level did not

reach statistical significance, probably because of the small number of patients. Idiopathic and exercise-induced anaphylactic episodes are known to be difficult to prevent because they are not predictable or regular in their appearance. In particular, pediatric idiopathic anaphylaxis can manifest at any age and can be quite severe.¹⁹ Therefore, it is important to recognize this condition in children so that it may be appropriately treated; specific therapy with epinephrine has been shown to prevent the potentially fatal consequences of anaphylaxis.¹⁹

Similar to our previous studies,^{1,5,20} our current investigation showed that, in Italy, the availability of epinephrine, despite appropriate education, is still limited in this patient population. Our data revealed that only approximately 40% of the patients with a previous episode of anaphylaxis still had epinephrine available after 7 years. This finding is even more worrisome because between 10% and 20% of the patients may have had expired or broken devices, as reported by Sicherer et al.²⁰ The high cost of Fastjekt, which is not reimbursed by the national health system, may partially explain this phenomenon, but the general belief among the population, general practitioners, and pharmacists that epinephrine is a very dangerous drug may also contribute to this finding. The difficulties in teaching the use of epinephrine and in convincing patients to have it available are a universal problem.^{20,21} Often, even physicians do not know how to use the self-injectable epinephrine.²⁰

CONCLUSION

The data from this study highlight the need to educate and to monitor closely pediatric patients with food allergy and anaphylaxis and to increase our efforts to instruct them in the appropriate use of epinephrine. Most deaths due to food-related anaphylaxis occur because of the accidental ingestion of foods known by patients to cause allergic reactions and because of the unavailability of epinephrine at the moment of the event.⁸ The availability of epinephrine for treatment of anaphylaxis was low among children in our study population. We also found that patients may have a greater risk of recurrence of anaphylaxis if they have AD, OA, or at least 1 positive result of skin prick tests to food allergens. Further, related studies are needed.

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